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Echocardiographic Correlates of Survival in Patients With Chest Pain

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Objectives. This study sought to identify echocardiographic predictors of survival in patients with chest pain and to assess the utility of qualitative echocardiographic data in the prognostic stratification of this cohort.

Background. The potential usefulness of echocardiographic data in prognostic stratification of patients with acute chest pain is unclear, in part because of the qualitative nature of routinely available echocardiographic readings.

Methods. The study group comprised 513 patients who underwent transthoracic two-dimensional and Doppler echocardiography within 1 month of emergency department visits for acute chest pain. Clinical and electrocardiographic (ECG) data were recorded for these patients at the time of their initial evaluations, and echocardiographic data were subsequently obtained from the official hospital reports. Follow-up survival rate data were obtained from medical records or the Massachusetts Bureau of Vital Statistics.

Results. A mean of 28.5 months after the index visit, 102 patients (20%) had died, including 58 (57%) for whom the primary cause of death was cardiovascular. In analysis of routinely available qualitative echocardiographic data, left ventricular size and function, the presence of regional wall motion abnormalities, mitral regurgitation and structural abnormalities of the mitral valve were significant univariate correlates of both overall mortality and death from cardiovascular causes. Severe left ventricular dysfunction (adjusted rate ratio 3.8, 95% confidence interval [CI] 1.9–7.5) and moderate or severe mitral regurgitation (adjusted rate ratio 2.4, 95% CI 1.5–3.7) were independent predictors of mortality in a multivariate Cox regression analysis that adjusted for clinical and ECG variables. Moderate or severe left ventricular dysfunction and mitral regurgitation were predictors of mortality in the subset of patients without acute myocardial infarction.

Conclusions. Qualitative echocardiographic reports of left ventricular dysfunction and mitral regurgitation were independent correlates of prognosis in patients with acute chest pain, including patients without acute myocardial infarction. Further data are needed to assess the generalizability of these findings and the implications for use of this diagnostic technology.

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Transthoracic two-dimensional, Doppler echocardiography is a widely utilized and readily available method for assessing left ventricular function and other cardiac abnormalities that have been identified as predictors of outcome after acute myocardial infarction (1–8). However, the role of echocardiography in the evaluation of the larger population of patients who present with acute chest pain is less clear.

This uncertainty may be due in part to the time-consuming nature of quantitative echocardiographic analysis and the reliance on qualitative data in routine clinical interpretation. For example, at many, if not most, institutions, echocardiographic assessments of left ventricular function are categorized as normal or as slightly, moderately or markedly abnormal. Similarly, mitral regurgitation is often categorized on a scale from 0 to 4+. Such qualitative measurements have generally not been integrated into risk stratification algorithms, which have more frequently used quantitative assessments of the ejection fraction obtained from radionuclide studies or cardiac catheterization.

To assess the utility of routinely available qualitative echocardiographic data in the prognostic stratification of patients with acute chest pain, we studied patients who presented to the emergency department of an urban teaching hospital with a chief complaint of chest pain. The findings have implications for the application and interpretation of echocardiographic data in this population.

Methods

Study patients. All 2,514 patients ≥30 years old who presented to the emergency department of Brigham and

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Women's Hospital for evaluation of acute chest pain not explained by trauma or chest X-ray findings in 1987 to 1989 were eligible for the Chest Pain Study, a multiphase investigation of optimal diagnostic and management strategies in this population. This report includes the 513 patients (20%) who underwent transthoracic two-dimensional and Doppler echocardiographic evaluation within 1 month of their emergency department evaluation. These echocardiographic studies were ordered and performed at the discretion of the patient's physician. Therefore, the subset of patients who are the focus of this report do not represent a random subset of the overall population.

Data collection. For each patient, detailed clinical data from the history, physical examination and electrocardiogram (ECG) were recorded prospectively by the emergency department physician or by a research nurse using the data collection protocol of the Chest Pain Study (9–17). The ECG findings were considered new unless their presence on previous ECGs could be confirmed. At the time of data collection, the person completing the form was unaware of the patient's outcome and could not be influenced by knowledge of the patient's course after leaving the emergency department.

Follow-up data. For patients who were admitted to the hospital, data on complications and procedure utilization were recorded by a research nurse who performed daily reviews of the medical record. Data on long-term survival rate and the cause of death were collected by review of medical records and death certificate records at the Massachusetts Bureau of Vital Statistics. Deaths attributed directly to cardiac causes, including myocardial infarction, congestive heart failure or cardiomyopathy and arrhythmia, were considered cardiovascular deaths. In addition, sudden deaths were assumed to be cardiac in origin unless specific information to the contrary was available (e.g., cardiac arrest in the setting of sepsis and gangrenous bowel was coded as noncardiac death). Follow-up data of at least 1 year in duration were obtained for 445 (87%) of the 513 patients, including 67 patients who died during the first year. The average length of follow-up was 28.5 months (range 0 to 58).

Echocardiographic data. Echocardiographic studies were performed a median of 2 days after the index visit (range 0 to 28). Data were obtained from the official reports generated at the time of the procedure. Qualitative categoric data such as those routinely provided in clinical practice were available concerning left ventricular size, function and hypertrophy, each of which was coded as normal or as mildly, moderately or severely abnormal. Other data included the presence or absence of wall motion abnormalities and significant structural and functional aortic and mitral valve disease. Although specific information with regard to the criteria used by the individual clinical readers is not available, general guidelines for echocardiographic interpretation in the Brigham and Women's Hospital Noninvasive Laboratory were as follows: left ventricular function was graded as normal (estimated ejection fraction >50%), mildly (ejection fraction 40 to 50%), moderately (ejection fraction 30 to 40%) or severely (ejection fraction <30%) depressed. Regional wall motion abnormalities were considered present if focal areas of hypokinesia, akinesia or dyskinesia could be identified. Left ventricular hypertrophy was present when wall thickness was ≥12 mm. Structural abnormalities of the mitral valve included prosthetic valves and myxomatous or rheumatically deformed valves, as well as less specific findings, such as leaflet thickening and leaflet or annular calcification, or both. Mitral regurgitation was qualitatively assessed on a 0 to 4+ scale and was based predominantly on color Doppler appearance of the jet in relation to left atrial size. Structural abnormalities of the aortic valve included prosthetic valves, thickened or calcified valves or, in one case, inability to visualize the valve adequately. Aortic insufficiency was graded on a 0 to 3+ scale, corresponding to none, mild, moderate and severe, on the basis of width of the jet in relation to the left ventricular outflow tract and the spatial extent of jet area. When variables were not mentioned in the echocardiographic report, they were assumed to be normal for that patient. If the severity of an abnormality was ambiguous (<2% of all variables coded), the tape was reviewed and classified by a single reviewer (K.E.F.) who was unaware of other clinical data for the patient at the time.

Definitions. Patients were considered to have ischemic changes on the initial ECG if the physician in the emergency department noted 1) probable new transmural infarction with ≥1-mm ST segment elevations or Q waves in two or more leads; 2) new ischemia or strain with ≥1-mm ST segment depression in two or more leads; or 3) other new ST segment or T wave changes of ischemia or strain. Acute myocardial infarction at the time of initial presentation was diagnosed if 1) characteristic evolution of serum enzyme levels occurred, including creatine kinase, MB fraction (CK-MB) detected in more than trace amounts by qualitative electropheretic assay or in amounts of at least 5% of total CK levels with a typical increase and decrease on quantitative assay, *or* 2) a level of lactate dehydrogenase isoenzyme 1 that was greater than that of lactate dehydrogenase 2 in the absence of hemolysis or renal infarction, *or* 3) an ECG showing development of new pathologic Q waves (at least 0.04 s in duration) and ≥25% decrease in the amplitude of the following R wave, compared with the emergency department ECG. The presence or absence of clinical complications was recorded prospectively from the medical record during daily chart reviews by a research nurse.

Data analysis. The univariate relations between echocardiographic variables and survival rates were assessed by means of univariate Cox regression analyses (18) using the SAS procedure PHREG, which were used to calculate mortality rate ratios comparing the unadjusted risk of mortality for patients with and without each echocardiographic finding. The overall cohort was also divided into subgroups on the basis of global left ventricular function (normal, mild, moderately or severely reduced) and degree of mitral regur-

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Table 1. Baseline Clinical Characteristics of Patients With and Without an Echocardiogram Within 1 Month of Presentation

	With Echocardiogram (n = 513)	Without Echocardiogram (n = 2,001)	p Value
Mean (±SD) age (yr)	62 ± 14	52 ± 14	< 0.001
Male gender	243 (47%)	973 (49%)	0.61
History of coronary artery disease	237 (46%)	552 (28%)	< 0.001
Rales on examination	149 (29%)	181 (9%)	< 0.001
Ischemic changes on ECG*	240 (48%)	270 (14%)	< 0.001
Shock	6 (1%)	2 (0.1%)	< 0.001
Acute myocardial infarction	107 (21%)	58 (3%)	< 0.001
Hospital admission†	470 (92%)	793 (40%)	< 0.001

*Electrocardiographic (ECG) data unavailable in 34 patients. †Information unavailable in seven patients. Data presented are number (%) of patients.

gitation (0 to 4+). Kaplan-Meier life table analyses (19) were used to calculate overall and cardiovascular mortality for each patient subgroup. In the analysis of cardiovascular mortality, patients who died of noncardiac causes were censored from analysis at the time of death.

Multivariate analyses of the incremental impact of echocardiographic data after consideration of clinical data were performed using Cox proportional hazard analyses. Clinical variables previously shown to be important for predicting long-term prognosis in this group were forced into the model (17). These variables were age, history of coronary artery disease, ischemic changes on the emergency department ECG and presence of rales or cardiogenic shock at the time of presentation or during admission. Additional candidate clinical and echocardiographic variables were entered into the model in a forward stepwise selection process using conventional entry and retention criteria of $p < 0.05$. These included clinical variables, such as diagnosis of unstable angina, myocardial infarction, congestive heart failure or pulmonary edema during the hospital period, and utilization of major procedures, such as Swan-Ganz catheterization, intraaortic balloon pump, percutaneous transluminal coronary angioplasty and coronary artery bypass grafting. Candidate echocardiographic variables were recoded as binary "dummy" variables corresponding to different cut points for multilevel categoric variables. For example, left ventricular dysfunction, initially coded in four levels (none, mild, moderate and severe), was recoded as three binary variables, one comparing normal function with any level of dysfunction, one comparing patients with no or mild dysfunction to those with moderate or severe dysfunction and one comparing patients with no, mild or moderate dysfunction with those patients having severe dysfunction. Echocardiographic variables that correlated with survival rate at a level of $p < 0.10$ in univariate Cox analysis were eligible for entry into the model. A similar multivariate analysis was also performed within the subset of 406 patients not having acute myocardial infarction at the time of presentation to the emergency department. Because both patients with shock in this subset died, and model convergence was therefore questionable, this variable was omitted from the subset analysis.

Results

Baseline characteristics. The 513 patients who underwent echocardiography (mean [±SD] age 62 ± 14 years, 47% male) were in several ways at higher risk for cardiac complications than the 2,001 patients who did not undergo this test during the 1st 30 days after this presentation (Table 1). More than 40% of patients undergoing echocardiography (46%) reported a history of previous coronary artery disease (angina or myocardial infarction) versus 28% in the remainder of the cohort. Patients who underwent echocardiography were more likely to present with rales and to have ischemic changes on the initial ECG. Ninety-two percent of patients who underwent echocardiography were admitted to the hospital after their presentation to the emergency department, and 21% were diagnosed with acute myocardial infarction during their index presentation.

At follow-up (mean 28.5 months), 102 (20%) of the patients who underwent echocardiograms had died, including 58 (57%) for whom the primary cause of death was cardiovascular. A total of 67 deaths (66%) occurred during the first year after presentation to the emergency department, including 41 of the cardiovascular deaths (71%).

Univariate correlates of survival. *Total mortality.* In univariate Cox analyses, several echocardiographic variables were significant correlates of overall mortality (Table 2). These correlates included structural abnormalities of the mitral and aortic valves, aortic insufficiency, mitral insufficiency, left ventricular enlargement, moderate or severe depression of global left ventricular function and the presence of regional wall motion abnormalities. For global left ventricular function and mitral regurgitation, mortality in Kaplan-Meier lifetable analysis increased steadily with the severity of the abnormalities (Fig. 1 and 2). The highest mortality rate ratios were found for severe left ventricular enlargement (5.8, 95% confidence intervals [CI] 2.5–13.5),

Table 2. Survival Rate in Relation to Echocardiographic Findings by Cox Univariate Regression Analysis

Variable*	Total No. of Pts.	Total Mortality			Cardiovascular Mortality		
		No. of Deaths	Rate Ratio†	p Value	No. of CVD	Rate Ratio†	p Value
Aortic valve							
Normal	251	36 (14%)	1.0	—	22 (9%)	1.0	—
Abnormal	258	64 (25%)	1.7 (1.1–2.6)	< 0.05	34 (13%)	1.5 (0.9–2.5)	NS
Mitral valve							
Normal	287	39 (14%)	1.0	—	23 (8%)	1.0	—
Abnormal	223	61 (27%)	2.1 (1.4–3.1)	< 0.0005	33 (15%)	1.9 (1.1–3.2)	< 0.05
LV enlargement							
None	382	59 (15%)	1.0	—	29 (8%)	1.0	—
Mild	76	20 (26%)	1.8 (1.1–3.0)	< 0.05	12 (16%)	2.2 (1.1–4.3)	< 0.05
Moderate	45	17 (38%)	2.8 (1.7–4.9)	0.0001	13 (29%)	4.3 (2.2–8.3)	0.0001
Severe	10	6 (60%)	5.8 (2.5–13.5)	0.0001	4 (40%)	7.4 (2.6–21.1)	0.0002
LV hypertrophy							
None	228	38 (17%)	1.0	—	30 (13%)	1.0	—
Mild	197	40 (20%)	1.2 (0.7–1.8)	NS	16 (8%)	0.6 (0.3–1.1)	NS
Moderate	74	17 (23%)	1.3 (0.7–2.3)	NS	7 (9%)	0.7 (0.3–1.6)	NS
Severe	10	4 (40%)	2.7 (0.9–7.5)	NS	2 (20%)	1.7 (0.4–7.1)	NS
LV dysfunction							
None	323	43 (13%)	1.0	—	17 (5%)	1.0	—
Mild	88	18 (20%)	1.6 (0.9–2.7)	NS	13 (15%)	2.9 (1.4–6.0)	< 0.005
Moderate	75	27 (36%)	3.2 (2.0–5.2)	0.0001	19 (25%)	5.5 (2.9–10.6)	0.0001
Severe	24	13 (54%)	7.1 (3.8–13.3)	0.0001	8 (33%)	10.1 (4.3–23.7)	0.0001
Mitral regurgitation							
None	266	27 (10%)	1.0	—	13 (5%)	1.0	—
1+	127	24 (19%)	2.0 (1.1–3.4)	< 0.05	13 (10%)	2.2 (1.0–4.7)	< 0.05
2+	97	38 (39%)	4.5 (2.7–7.4)	0.0001	21 (22%)	5.1 (2.6–10.2)	0.0001
3+/4+	15	9 (60%)	8.1 (3.8–17.3)	0.0001	7 (47%)	12.3 (4.9–31.0)	0.0001
Aortic regurgitation							
None	403	68 (17%)	1.0	—	40 (10%)	1.0	—
1+	86	26 (30%)	1.8 (1.1–2.8)	< 0.05	11 (13%)	1.3 (0.7–2.5)	NS
2+	15	4 (27%)	1.7 (0.6–4.7)	NS	3 (20%)	2.1 (0.7–6.9)	NS
3+	1	0	—	—	0	—	—
RWMA							
Absent	296	46 (16%)	1.0	—	21 (7%)	1.0	—
Present	215	56 (26%)	1.7 (1.2–2.6)	< 0.01	37 (17%)	2.5 (1.5–4.3)	0.001

*For each variable, occasional data were unavailable for all 513 echocardiograms because of technical limitations. †Numbers in parentheses are 95% confidence intervals. CVD = cardiovascular deaths; LV = left ventricular; Pts = patients; RWMA = regional wall motion abnormality.

severe left ventricular dysfunction (7.1, 95% CI 3.8–13.3) and 3+ or 4+ mitral regurgitation (8.1, 95% CI 3.8–17.3).

Cardiovascular mortality. Structural abnormalities of the mitral valve, left ventricular enlargement, left ventricular dysfunction of any degree, mitral regurgitation and the presence of regional wall motion abnormalities were significantly associated with cardiovascular mortality. As with overall mortality, a trend toward increasing risk of death

Figure 1. Kaplan-Meier survival curves for patients stratified by left ventricular function. LVD = left ventricular dysfunction.

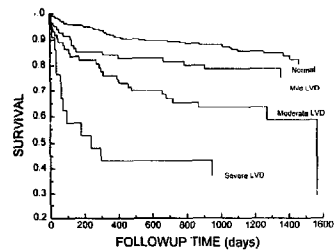

Figure 2. Kaplan-Meier survival curves for patients stratified by grade of mitral regurgitation (on a 4+ scale).

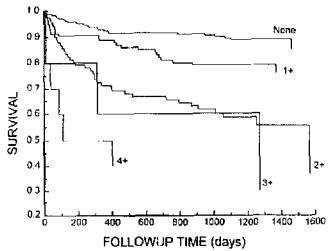

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Table 3. Independent Echocardiographic Predictors of Long-Term Survival Rate*

Variable	Rate Ratio (95% confidence interval) Mortality	Cardiovascular Mortality
LVD	—	2.7 (1.4–5.3)
Severe LVD	3.8 (1.9–7.5)	—
≥2+ Mitral regurgitation	2.4 (1.5–3.7)	2.4 (1.3–4.4)

*After adjustment for age, history of coronary artery disease, rales on physical examination, ischemic changes on electrocardiogram and shock. LVD = left ventricular dysfunction.

Table 4. Independent Echocardiographic Predictors of Long-Term Survival Rate in Subset of Patients Without Acute Myocardial Infarction

Variable	Rate Ratio (95% confidence interval) Mortality*	Cardiovascular Mortality†
Any LVD	—	5.2 (2.4–11.3)
Moderate/severe LVD	2.1 (1.2–3.6)	—
Mitral regurgitation	2.0 (1.2–3.5)	—

*Adjusted for age, history of coronary artery disease, rales on physical examination and ischemic changes on electrocardiogram (ECG). †Adjusted for age, history of coronary artery disease, rales on physical examination, ischemic changes on ECG and congestive heart failure during admission. LVD = left ventricular dysfunction.

with increasing level of abnormality was seen for left ventricular dysfunction, left ventricular enlargement and mitral regurgitation.

Multivariate analyses. In a multivariate Cox regression analysis (Table 3), two echocardiographic variables (left ventricular function and mitral regurgitation) were independently associated with mortality after adjusting for clinical factors, such as age ($p = 0.001$), history of previous angina or myocardial infarction ($p = 0.16$), rales on examination ($p = 0.003$), ischemic changes on ECG ($p = 0.37$) or shock ($p = 0.008$). Severe left ventricular dysfunction was associated with a 3.8-fold increase in the risk of death, even after inclusion of clinical factors. The presence of moderate or severe mitral regurgitation (i.e., mitral regurgitation graded as at least 2+, on a 0 to 4+ scale) was associated with a 2.4-fold increase in the risk of death.

For cardiovascular death, any level of left ventricular dysfunction was associated with a 2.7-fold risk of cardiac death, whereas mitral regurgitation at least moderate in severity was again associated with a 2.4-fold increase in the risk of cardiac death after adjusting for clinical factors. These included age ($p = 0.03$), history of angina or previous infarction ($p = 0.21$), rales on examination ($p = 0.10$), ischemic changes on ECG ($p = 0.24$) and shock ($p = 0.01$).

Subset analysis among patients without acute myocardial infarction. A subset analysis for the 406 patients who did not have an acute myocardial infarction during the index presentation to the emergency department indicated that left ventricular dysfunction and mitral regurgitation remained independent predictors of mortality (Table 4). Moderate or severe left ventricular dysfunction was an independent predictor of mortality after adjusting for clinical variables with a mortality rate ratio of 2.1. Mitral regurgitation of any degree was also associated with a twofold increase in the risk of death. For cardiovascular mortality, the presence of any degree of left ventricular dysfunction was associated with 5.2-fold increase in the risk of cardiac death.

Discussion

Although two-dimensional, Doppler echocardiography is one of the most commonly used cardiologic tests, its optimal role in the assessment of patients with chest pain remains uncertain. In this study we found that several echocardiographic variables correlated significantly with both overall and cardiovascular survival rate in these patients and that two semiquantitative factors (left ventricular function and mitral regurgitation) were independent predictors of mortality in patients with and without acute myocardial infarction, even when clinical and ECG data were taken into account.

These data are consistent with and extend findings from previous reports that have established global left ventricular function as a potent prognostic factor for patients after acute myocardial infarction (1–6). Tcheng et al. (7) and Lehman et al. (8) have previously reported that mitral regurgitation associated with acute myocardial infarction is an independent predictor of mortality, is linked to increased 1-year mortality and is often clinically silent. Other studies have reported a correlation between the extent of regional asynergy by echocardiography and predischarge complications, such as congestive heart failure, malignant ventricular arrhythmia or death, in patients admitted with acute myocardial infarction (20–23).

Most of these other studies have not addressed the extent to which these findings can be generalized to the larger population of patients who present with acute chest pain and are found not to have myocardial infarction. Furthermore, the incremental benefit of echocardiographic testing after consideration of routinely available clinical and ECG data is uncertain. Oh et al. (24) have described the potential utility of transthoracic two-dimensional and Doppler echocardiography in the emergency department in evaluating acute chest pain syndromes. More recently, Sabia et al. (25) reported their experience in 171 patients presenting to an emergency department with chief complaints of potentially cardiac origin, such as chest pain or shortness of breath. In multivariate analysis, they found a 30% increase in the likelihood ratio statistic for late cardiac events, such as serious arrhythmia, nonfatal myocardial infarction, coronary revascularization or cardiac-related death, in patients with left ventricular dysfunction on initial echocardiogram.

In this cohort, multiple variables including, but not limited to, left ventricular function were significantly associated

with both overall and cardiovascular mortality. Moreover, qualitative and semiquantitative echocardiographic assessment of mitral regurgitation was an independent predictor of mortality in multivariate analysis, even after adjusting for information available from the history, physical examination and ECG. Whether significant mitral regurgitation serves to mask or diminish the apparent severity of underlying ventricular dysfunction or whether mitral regurgitation itself is associated with increased mortality by other mechanisms cannot be determined from these data.

Although the factors of left ventricular dysfunction and mitral regurgitation are predictive of both overall and cardiovascular mortality, any level of dysfunction was associated with cardiovascular mortality, whereas only severe dysfunction was predictive of overall mortality. It may be that ventricular dysfunction has greater prognostic value for the more specific end point of cardiovascular mortality than for the more general end point of all-cause mortality.

Echocardiographic interpretation. Echocardiographic data in this study were taken directly from the routine clinical reports generated at the time of testing. These data suggest that even qualitative categoric evaluation of left ventricular function, uncorrected for interobserver variability, may provide important prognostic information. Although more detailed information with regard to quantitation of left ventricular function, such as calculation of ejection fraction from M-mode measurements or wall motion scoring, is routinely provided at some institutions and may provide additional prognostic information, such qualitative data are widely available in both teaching and community-based hospitals. Furthermore, multiple studies have addressed the limitations of assessing the severity of regurgitant lesions, such as mitral insufficiency, on the basis of echocardiographic variables, particularly color flow Doppler (26,27). Although color flow variables such as jet size have been shown to correlate well with angiographic grade of mitral regurgitation (28), the correlations between these variables and hemodynamic indicators, such as angiographically derived regurgitant volume and regurgitant fraction, are weaker (27) and may be affected by technical factors (29,30). Despite the difficulties inherent in these measures, Doppler echocardiographic information concerning the presence and severity of mitral regurgitation provided prognostic information in addition to clinical factors in this study.

Clinical implications. Our data suggest that routinely available two-dimensional and Doppler echocardiographic data can provide useful incremental risk stratification information concerning survival rate in patients presenting with chest pain. The findings should not be interpreted as a recommendation that this test be performed routinely for all patients with chest pain because several factors may limit their generalizability. The cohort described in this study underwent echocardiography on clinical grounds and were evaluated at a single urban teaching hospital. Whether findings from this group can be generalized to all patients with acute chest pain remains to be determined. In addition, follow-up data on survival status at 1 year could be obtained for 87% of the cohort, and it is conceivable that the 13% of patients for whom follow-up was not obtained differed in a systematic fashion from the remainder of the cohort, introducing a potential bias. Furthermore, the impact on management and outcome of patients of this additional prognostic information is unknown.

A prospective cohort study is currently underway to determine whether these findings can be generalized to a different, unselected group of patients and to explore the potential role of transthoracic echocardiography in risk stratification for both short-term complications and long-term survival and health status outcomes. Should these investigations confirm an incremental benefit of testing in this population or its subsets, evaluation of the cost-effectiveness of management strategies incorporating two-dimensional and Doppler echocardiography would be indicated.

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